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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/651,290	08/30/2000	Marcin S. Filutowicz	P00154US/13238/00016	2591

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/651,290	FILUTOWICZ, MARCIN S.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 16-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12 and 16-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17&18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 13, 2003 has been entered.

2. Applicant's amendment is acknowledged. Claims 1-12 and 16-27 have been amended. Claims 13-15 and 28-30 have been cancelled.

3. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

New Grounds of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-12 and 16–27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

The claims are drawn to a recombinant bacterium which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and at least one screenable marker gene. The amended claims contain new matter. Applicant has amended the claimed invention from an antibacterial agent to a recombinant bacterium. Applicant has not set forth where in the instant specification that support can be found for the amended claims.

The following rejection under 112, first paragraph is maintained because of Applicant's assertion that the claims are now drawn to an recombinant bacterium which is assumed to be the same as the antibacterial agent since the process by which the recombinant bacterium is obtained is the same as the process by which the antibacterial agent was obtained. Since Applicant has not direct the Examiner to the section of the instant specification where the amendment is supported it is unclear as to if the antibacterial agent and the recombinant bacterium are one in the same. Therefore, the above new matter rejection is set forth above.

Rejection Maintained

4. The rejection under 35 U.S.C. 112, first paragraph is maintained for the reasons of record as set forth on pages 3-11 of the Final Office Action (paper no. 14, mailed July 12, 2002).

The rejection was on the grounds that the specification contained subject matter which was not described in the in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and optionally, at least one screenable marker gene and a pharmaceutical preparation comprising the antibacterial agent.

The specification generically claims an antibacterial agent that comprises a non-pathogenic donor bacterial cell harboring at least one transmissible plasmid comprising an origin of replication, an origin of transfer and optionally at least one screenable gene marker. The claimed invention further includes a plurality of microorganisms of which the donor cell or recipient cell can be obtained. The specification does not provide substantive evidence that the claimed antibacterial agent can maintain stability or that the pharmaceutical preparation comprising the antibacterial agent is capable of treating bacterial infections. This demonstration is required for the skilled artisan to be able to use the claimed invention for the intended purpose of treating bacterial infections. Without this demonstration, the skilled artisan would not be able to reasonably predict whether the claimed invention could survive *in vivo* use or whether the artisan would be able to predict if the administration of the claimed pharmaceutical preparation, would be able to treat bacterial infections.

There are several factors that contribute to the stability of plasmids that are well known in the art. These factors include: 1) the ability of conjugative transfer within and between genera, 2) essential components required to ensure stabilization 3) mating pair stabilization and 4) compatibility between the donor and recipient cell. The ability to reasonably predict the capacity of plasmids to be conjugatively transferred within genera and especially between genera, maintain stability is problematic. This is evidenced by Ambrozic et al, *Microbiology (ENGLAND), February 1998, 144(Pt 2), p. 343-352).* Ambrozic et al teach that conjugal transfer was demonstrated with low frequency to *Klebsiella pneumoniae* suggesting that a natural barrier effectively bars transfer. Specific sequences are also required for the complete stabilization of plasmids. For example, Roberts et al, *(Journal of Bacteriology, November 1990, 172 (11), p. 6204-6216)* teach that one of the regions responsible for stable inheritance of the broad host range plasmid RK2 is contained within the PstI C fragments. Robert et al teach that the PSTI C fragment itself is not required for stabilization activity, however

the PSTI C fragment encodes a multimer resolution system which required adjacent sequence to maintain complete stabilization. Mating stabilization during conjugative transfer between the donor and recipient cell is also required. Klimke et al, *(Journal of Bacteriology, August 1998, 180 (16), p. 4036-4043)* teach that mating stabilization occurs during conjugative transfer whereby the donor cell and recipient cells form a tight junction which requires pili as well as TraN and TraG (proteins involved in matting pair stabilization) in the donor cell. Klimke et al teach that the TraN and not the F pili appears to interact with OmpA and LPS moieties during conjugation, resulting in mating stabilization. Klimke et al further teach that this is the first step in efficient mobilization of DNA. Compatibility between the donor cell and the recipient cell is also necessary. This is further evidenced by Rahal et al, *(Annales de microbiologie (FRANCE), May-June 1978, 129 (4), p. 409-414).* Rahal et al teach that very few multi-resistant strains of *Vibrio cholerae* have been isolated this may be due to a high frequency of plasmids being lost due to the incompatibility of groups. Since genetic mutations are used to determine the structural and functional properties of the claimed antibacterial agent and pharmaceutical composition the predictability of which changes or mutations can be tolerated in the host and still retain similar activity requires a knowledge of and guidance with regard to which mutations can be made in the plasmid wherein stability will be maintained. The cited references have shown that unpredictability exists regarding plasmid stability. Therefore, it can be concluded that undue experimentation would be required to make and use the claimed antibacterial agent without proper guidance.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the pharmaceutical preparation commensurate in scope with these claims. The specification fails to teach how to make and use the claimed pharmaceutical preparation. The term "pharmaceutical" encompasses the ability of the specific antigen to induce protective immunity to a host. The specification does not disclose how to formulate the pharmaceutical preparation or what dosages are required to treat a patient with a bacterial infection? The specification further does not disclose whether the antibacterial agent can be survive the mouth, stomach or intestines without being degraded or if the antibacterial agent is capable of reach the target organs necessary to treat a particular bacterial infection. Therefore, it is unclear as to how to formulate a pharmaceutical preparation comprising the antibacterial agent which will treat **any** bacterial infection.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting a stable antibacterial

agent and pharmaceutical preparation that would achieve a desire level of success when administered to a patient with a bacterial infection that is capable of treating that bacterial infection, 3) there are limited working examples which suggest the desired results of a antibacterial agent that is to be used in a pharmaceutical preparation to treat any bacterial infection, 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

Applicant urges that the claims as amended are drawn to a recombinant bacterium which has utilities other than in pharmaceutical preparations for use in treatment of humans and further that stability of the plasmid in either the donor or the recipient is not critical to the operation of the invention as claimed. Applicant urges that the more important parameter is that the bacteria are capable of conjugatively transferring the plasmid to a recipient cell and that such cells can be prepared immediately prior to performing the conjugation wherein there would be substantially little opportunity for plasmid loss from donor cells. Applicant urges that it is expected that recipient cells would be substantially prevented from further multiplying due to the effects of the runaway plasmid or killer gene transferred to the recipient during conjugation. Applicant urges that the specification teaches the use of killer plasmids and also teaches that both *ori* and *tra* sequences are required. Applicant urges that the specification teaches that conjugation requires contact between the cells and that the transfer of genetic traits can be mediated by many plasmids and the specification teaches several examples from a number of different bacteria. Applicant urges that the claimed invention is not claiming methods of use instead the claimed invention is a

novel composition of matter that has specific, substantial and credible utilities that are recited in the specification.

Applicant's arguments filed May 13, 2003 have been fully considered but they are not persuasive. It is the Examiner's position that the claims as amended required the same process as the originally presented claims and therefore, the utilities of the amended claims would then be the same as the originally present claims. The claims are drawn to an recombinant bacterium which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication, an origin of transfer and at least one screenable marker gene wherein the donor cell further comprises one or more transfer genes conferring upon the donor cell the ability to conjugatively transfer the transmissible plasmid to the recipient cell and wherein the donor cell produces the plasmid replication repressor and further wherein at least one recipient cell is a pathogenic bacterium that does not produce the plasmid replication repressor, thereby enabling the transmissible plasmid to undergo runaway replication in the recipient cell. Despite the knowledge in the art for using recombinant techniques to produce recombinant bacteria, the specification fails to specifically point out how to make and use the claimed invention. The claimed invention encompasses the use of any bacteria, which includes the genera *Klebsiella.* The prior art teaches that the ability to reasonably predict the capacity of plasmids to be conjugatively transferred within genera and especially between genera, maintain stability is problematic. This is evidenced by Ambrozic et al. Ambrozic et al teach that conjugal transfer was demonstrated with low frequency to *Klebsiella pneumoniae* suggesting that a natural

barrier effectively bars transfer. The claimed invention requires the transfer of a "transmissible plasmid" from a donor cell to a recipient cell. A toxic or killing effect cannot occur if the transmissible plasmid" is not conjugatively transferred from the donor cell to the recipient cell. Therefore, in view of the teaching of Ambrozic et al one can reasonably assume that the capacity of plasmids to be conjugatively transferred within and between all genera of bacteria is unpredictable. Since the claimed invention is directed to any bacterial donor and any recipient cell, the Klimke et al reference was cited to point out that mating stabilization during conjugative transfer between donor and recipient cell is required. Roberts et al teach that one of the most important survival characteristics of naturally occurring plasmids the ability to ensure that both progeny of a cell division contain at least one copy of the plasmid and this is often accomplished in spite of a very low number of plasmid copies per cell. Roberts et al teach that the replication control mechanism to ensure a constant number of plasmid copies per chromosome which provides a pool of plasmids for segregation to each daughter cell is crucial. Therefore, one skill in the art can reasonable assume that stabilization is necessary for conjugative transfer of a "transmissible plasmid" from a donor cell to a recipient cell wherein the result is runaway replication in the recipient cell. Rahal et al teach that very few multi-resistant strains of *Vibrio cholerae* have been isolated; this may be due to a high frequency of plasmids being lost due to the incompatibility of groups. Since genetic mutations are used to determine the structural and functional properties of the claimed recombinant bacterium the predictability of which changes or mutations can be tolerated in the host and still retain similar activity requires a

knowledge of and guidance with regard to which mutations can be made in the plasmid wherein stability will be maintained. The cited prior art references have shown that unpredictability exists regarding plasmid stability, compatibility of the donor and recipient cells and the high frequency of plasmids being lost due to the incompatibility of groups. The instant specification has failed to provide enablement for the use of any non-pathogenic conjugative donor bacterium and the use of any recipient bacterium or the use of any transmissible plasmid to arrive at the claimed invention. The instant specification is limited in its guidance that would allow the skilled artisan to arrive at the claimed invention. While it is true that the claimed invention is drawn to a product and not a method of use, however, due to the lack of guidance found in the instant specification and the teaching of the prior art, it can be concluded that undue experimentation would be required to make and use the claimed recombinant without proper guidance. Therefore, the broadly claimed invention does not meet the enablement requirement which is set forth under 35 U.S.C. 112, first paragraph.

Status of Claims

5. No claims allowed.

Conclusion

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
July 23, 2003

NITA MINKFIELD
PRIMARY EXAMINER
4/24/03